REMARKS

Applicants have shown that human gliomas express a human IL13 (hIL13)-specific receptor that specifically binds IL13 with a greater affinity than it binds human IL4 (hIL4), and that intratumoral injection of cytotoxin-coupled hIL13 into animals bearing actively growing gliomas caused a significant reduction in the growth rate of the tumors. In some cases, this treatment eliminated any detectable tumors in such animals.

Application Status

Claims 1, 2, 4-6, and 14-22 were pending in the subject application. Claims 1 and 18 have been amended, and no claims have been cancelled or added. Therefore, claims 1, 2, 4-6, and 14-22, as amended, remain before the examiner for consideration.

First Rejection Under 35 USC 103

In the Office Action, claims 1, 2, 4-6 and 14-22 were newly rejected under 35 U.S.C. 103 as being unpatentable over US Patent No. 5,614,191 (the "191 patent") in view of Debinski et al. (JBC, 1996, 271:22428-22433; the "Debinski Paper") and further in view of BioCentury Extra (1996, 465:1; the "BioCentury Article") as evidenced by Debinski et al., Abstract, 17th International Cancer Congress, Rio de Janeiro, 1998 (the "Abstract"). Regarding the Abstract, the Office Action stated that:

> Given the findings of Debinski et al, Abstract, 17th International Cancer Congress, it is an inherent property of the receptors to be overexpressed in situ on GBM since Debinski specifically shows that the receptors are overexpressed in primary slice samples of GBM. The combined references teach as set forth previously and above, but do not teach the tumor is located in the cranium, do not teach intratumor administration of the molecule.

and

Finally, given the Debinski et al 1998 findings, it is clear that overexpression of the receptor *in situ* is an inherent property of the receptor on GBM.

The Office Action did not rely on the Abstract as a prior art reference to arrive at this rejection. Without relying on the Abstract, however, no prima facie case of obviousness can be established.

To establish a prima facie case of obviousness, a number of requirements must be met. Among these, the prior art relied on, coupled with the knowledge generally available in the art at the time of the invention, must provide the skilled artisan some motivation or incentive to modify a reference to arrive at Applicants' invention. See In re fine, 837 F.2d 1071, 1074 (Fed. Cir., 1988); In re Skinner, 2 USPQ2d 1788, 1790 (Bd. Pat. App. & Int., 1986). In addition, to establish a prima facie case of obviousness, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209 (Fed. Cir. 1991).

Amended independent claims 1 and 18 respectively refer to "[a] method of reducing the rate of growth of glioma cells in vivo in a mammalian subject..." and "[a] method of killing a glioma cell in situ...." Amended claim 1 recites the step of: "delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells," and amended claim 18 recites the step of: "contacting the glioma cell contained within the cranium of the mammalian subject with the molecule [i.e., a molecule having an IL13-moiety and a cytotoxic moiety] in an amount effective to kill the glioma cell." While the Abstract (not relied on for this rejection) might provide evidence that IL13 receptors are expressed on glioma cells in vivo/in situ, neither the '191 patent, the Debinski Paper, or the

BioCentury Article teaches anything about IL13R expression in vivo or in situ.

The '191 patent presents in vitro data relating to renal, colon, skin, and stomach cancer cell lines. Nowhere, however, are the terms "glioma" or "brain" even mentioned. The Debinski Paper discloses that established glioma cell lines and primary cultures of glioblastoma multiforme cells are sensitive to hIL13-based toxins in in vitro assays. None of the experiments of the Debinski Paper, however, were performed in situ. As previously indicated, there are significant differences between in vitro assays and the in situ/in vivo situation. The BioCentury Article describes a carmustine-containing polyanhydride wafer for implant into the brain of patients with glioblastoma multiforme, and teaches that the latter is a common form of brain cancer. It is entirely silent with respect to IL13.

A significant difference between the subject matter claimed in claims 1 and 18 and what is claimed in the '191 patent is that former refers to glioma cells while the '191 patent does not. Although glioma cells are mentioned in the Debinski Paper, the relevant experiments presented showed only that established glioma cell lines and primary cultures of glioblastoma multiforme cells are sensitive to hIL13-based toxins in in vitro assays. To arrive at the claimed invention, the Office Action apparently argued that the '191 patent and the Debinski Paper can be combined in a manner which suggests that gliomas express high levels of an IL13 receptor in vivo/in situ, and that from this suggestion an artisan skilled in the field of the invention, at the time the invention was made, would have expected that administering a molecule having an IL13-moiety and a cytotoxic moiety to a subject would reduce the rate of growth of the glioma cells or kill such cells. The '191 patent and the Debinski Paper, however, nowhere teach that anything about IL13 receptor expression in vivo/in situ. And, as previously set forth, the '191 patent (at page 7, lines 2-12) actually teaches away from this by indicating that prior studies showed that

overexpression of a molecule observed in in vitro cell cultures did not occur in the in situ situation. The Office Action addressed this argument by stating:

> The argument has been considered but has not been found persuasive because it is clear from Debinski et al, 1996, that the explant cells do not lose expression of the hIL13R antigen and that the antigen is expressed at a concentration ten times more than that found in the cell lines (see p. 22433, col 1, last paragraph). Contrary to Applicant's arguments, given the extensive overexpression of the receptor in the tumor explant, it would be expected that the antigen would be extensively overexpressed *in situ* and one would have expected to successfully treat a mammal with the method of the combined references. Finally, given the Debinski et al 1998 findings, it is clear that overexpression of the receptor *in situ* is an inherent property of the receptor on GBM.

Applicants believe this statement relies on inappropriate hindsight-fashioned logic in concluding the crucial point that " ...explant cells do not lose expression of the hIL13R antigen...." In making this statement, the Office Action has assumed that glioma cells in situ/in vivo express the same or more of this antigen. The evidence for making this assumption, however, is not provided by any of the references used to arrive at the rejection. Implicitly recognizing this lack of evidence, the Office Action refers to (but does not rely on) the Abstract in support of its argument.

Applicants also note that the "explant cells" the Office Action refers to are not simply cells that were removed from a patient and immediately tested for IL13 receptor expression. Rather "explant cells" were cells treated to several processing steps and then cultured in an RMPI1640-based medium in a humidified incubator. See page 22429, column 1, fourth paragraph. Hence, the phrase "explant cells" refers to an in vitro cell culture and not a freshly excised tissue sample. Thus, without relying on the teachings of the Abstract, at the time the invention was made, it was simply not known whether glioma cells expressed IL13 receptors in

vivo or in situ.

Accordingly, given that (1) there was significant uncertainty as to whether glioma cells expressed IL13 receptors in situ/in vivo at the time the invention was made and (2) that the invention is within an unpredictable art (i.e., biotechnology), at most, at the time the invention was made, the combination of the '191 patent, the Debinski Paper, and the BioCentury Article might possibly have made it obvious to try using an IL13-cytotoxin fusion protein to reduce glioma growth in an animal. Being "obvious to try," however, is not the standard under 35 U.S.C 103. See In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Thus, because (1) the Abstract has not been relied upon for this rejection, and (2) the combination of '191 patent, the Debinski Paper, and the BioCentury Article alone fail to indicate or suggest that glioma cells express IL13 receptors in vivo or in situ, applicants submit that the Office Action has not made out a prima facie case of obviousness, and respectfully request withdrawal of this rejection.

Second Rejection Under 35 USC 103

Claims 1, 2, 4-6 and 14-22 were also rejected under 35 USC 103 as being unpatentable over the combination of the '191 patent, the Debinski Paper, the BioCentury Article, and the Abstract. Accompanying this amendment are declarations of the present inventors declaring that they were the only inventors of the subject matter described in the Abstract. For the reasons stated above, absent the availability of the Abstract as a prior art reference, a prima facie case of obviousness cannot be made out. Applicants also note that the BioCentury Article does not teach or suggest intratumoral injection. Accordingly, withdrawal of this rejection is requested.

Rejection under 35 USC §112

Claims 1, 2, 4-6, and 14-22 were rejected under 35 USC 112, first paragraph, as the specification allegedly did not contain a written description of the claimed invention. In particular, the Office Action stated:

> The limitation of a receptor that binds IL 13 but not IL4 has no clear support in the specification and the claims as originally filed....There is no mention of a receptor that specifically binds IL13 but not IL4. Given the definition of an IL13-specific receptor, it is clear that both IL13 and IL4 bind specifically to an IL13-specific receptor but that the affinity of IL13 is greater than the affinity of IL4.

Independent claims 1 and 18, from which the remainder of the claims depend, have been amended to recite: "...an IL13-specific receptor that binds IL13 with a greater affinity than it binds IL4...." Applicants believe the Office Action's indication that this phraseology is clear means that use of this language would satisfy the written description requirement of section 112. Accordingly, withdrawal of this rejection is requested.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

A petition for a one moth retroactive extension of time and the required fee are enclosed. The Commissioner is hereby authorized to charge any underpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

Applicants invite the Examiner to call the undersigned if clarification is needed on any matter within this Amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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J. Rodman Steele, Jr.
Registration No. 25,931
Stanley A. Kim, Ph.D., Esq.
Registration No. 42,730
AKERMAN SENTERFITT
222 Lakeview Avenue, Suite 400
Post Office Box 3188
West Palm Beach, FL 33402-3188
Telephone: (561) 653-5000

APPENDIX A

1. (Twice Amended) A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject, the glioma cells comprising an IL13-specific receptor that [specifically] binds IL13 [but not] with a greater affinity than it binds IL4, comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

18. (Amended) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell, the glioma cell comprising an IL13-specific receptor that [specifically] binds IL13 [but not] with a greater affinity than it binds IL4;

(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and

(c) contacting the glioma cell contained within the cranium of the mammalian subject with the molecule in an amount effective to kill the glioma cell.

APPENDIX B

1. (Amended) A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject, the glioma cells comprising an IL13-specific receptor that specifically binds IL13 with a greater affinity than it binds IL4, comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

2. (Amended) The method of claim 1, wherein the glioma cells are glioblastoma multiforme cells.

4. (Amended) The method of claim 1, wherein the glioma cells form a tumor in the mammalian subject and the growth of the tumor is inhibited.

5. (Amended) The method of claim 4, wherein the tumor volume is reduced.

6. (Amended) The method of claim 4, wherein the molecule is delivered by intratumoral injection.

14. (New) The method of claim 4, wherein the tumor is located in the cranium of the mammalian subject.

15. (New) The method of claim 14, wherein the IL13-moiety is hIL13.

16. (New) The method of claim 14, wherein the cytotoxic moiety is a Diphtheria toxin.

17. (New) The method of claim 14, wherein the cytotoxic moiety is a Pseudomonas toxin.

18. (New) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell, the glioma cell comprising an IL13-specific receptor that specifically binds IL13 with a greater affinity than it binds IL4;

(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and

(c) contacting the glioma cell contained within the cranium of the mammalian subject with the molecule in an amount effective to kill the glioma cell.

19. (New) The method of claim 18, wherein the glioma cell is a glioblastoma multiforme cell.

20. (New) The method of claim 18, wherein the IL13-moiety is hIL13.

21. (New) The method of claim 18, wherein the cytotoxic moiety is a Diphtheria toxin.

22. (New) The method of claim 18, wherein the cytotoxic moiety is a Pseudomonas toxin.